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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/699,243	10/27/2000	Isabel D.C. Markl	47675-238	5397

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EXAMINER	
GOLDBERG, JEANINE ANNE	
ART UNIT	**PAPER NUMBER**
1634	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	09/699,243	MARKL ET AL.	
	Examiner	Art Unit	
	Jeanine A. Goldberg	1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *19 October 2007*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1, 4, 7-8, 10-13, 15-19* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,4,7,8,10-13 and 15-19* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on October 19, 2007 has been entered.

2. This action is in response to the papers filed October 19, 2007. Currently, claims 1, 4, 7-8, 10-13, 15-19 are pending. All arguments have been thoroughly reviewed but are deemed non-persuasive for the reasons which follow.

3. Any objections and rejections not reiterated below are hereby withdrawn in view of the amendments to the Claims, applicants' arguments.

4. This action is FINAL.

Claim Rejections - 35 USC § 112- Enablement

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

5. Claims 1, 4, 7-8, 10-13, 15-19 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Factors to be considered in determining whether a disclosure meets the enablement requirement of 35 USC 112, first paragraph, have been described by the court in *In re Wands*, 8 USPQ2d 1400 (CA FC 1988). *Wands* states at page 1404,

> "Factors to be considered in determining whether a disclosure would require undue experimentation have been summarized by the board in Ex parte Forman. They include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims."

The nature of the invention and breadth of claims

The claims are drawn to performing a methylation assay on DNA to determine the methylation state of "a CpG dinucleotide" as indicative of diagnosis or prognosis of breast cancer, for example. The instant specification teaches hypermethylation refers to the methylation state corresponding to an increased presence of 5-mCyt at one or a plurality of CpG dinucleotides within a DNA sequence of a test DNA sample relative to the amount of 5-m-Cyt found at corresponding CpG dinucleotides within a normal control DNA sample.

The invention is in a class of invention which the CAFC has characterized as "the unpredictable arts such as chemistry and biology." Mycogen Plant Sci., Inc. v. Monsanto Co., 243 F.3d 1316, 1330 (Fed. Cir. 2001).

The unpredictability of the art and the state of the prior art

The art clearly illustrates that certain genes, including GSTP1, HIC-1, and p16, are hypermethylated and this is indicative of certain cancers (US Pat. 5,552,277; 5,846,712; 5,856,094).

In CACNA1G (see Toyota et al. Cancer Research, Vol. 59, pages 4535-4541, September 1999), a detailed analysis was provided for CpG islands within the gene. The eight regions each behaved very differently. For example Regions 1 and 2 behaved in a concordant manner. Region 3 had either no methylation or very low levels of methylation. Regions 5, 6, 7 behaved differently than regions 1-3. Regions 4, 8 behaved differentially again. Thus, with regards to hypermethylation in cancer, the CpG region upstream of CACNA1G appears to be behave independently (page 4538, col. 1).

Pao et al. (Human Molecular Genetics, Vol. 10, No. 9, pages 903-910) teaches the EDNRB promoter displays heterogeneous site specific methylation patterns in normal and tumor cells. Pao analyzed 11 individual CpG sites located throughout the CpG island. The sites showed that specific sites with high methylation levels in several tumors are also methylation in normal tissues suggesting they might serve as foci for further de novo methylation (abstract). Figure 2 illustrates the methylation profile in the promoter in primary tissue samples. The data on the 11 individual CpG sites spanning the whole island demonstrated that several non-adjacent CpG sites showed high methylation in tumor tissues and some of the normal samples (page 904, col. 1). Pao teaches that increased methylation is found at CpG-130 the 5' most CpG dinucleotide analyzed which is located on the fringe of the CpG island (page 905, col. 1). Pao teaches CpG 336 remained resistant to hypermethylation even when adjacent CpGs

were highly methylated. Moreover Pao teaches that the findings showed that in the EDNRB 5' regulatory region, prostate, bladder and colon normal tissues have methylation patterns that are particular to each type of tissue (page 906, col. 1). Some sites within the CpG island appeared to be preferential targets for de novo methylation whereas others seemed to be protected from hypermethylation changes (page 906, col.1). Thus, the teachings of Pao suggest that analysis of a single dinucleotide would not allow predictable association absent further experimentation to determine the methylation pattern in the particular tissue types and in normal tissues. The individual sites in a particular island are not predictably associated with each other dinucleotide in the island. Moreover, normal tissues may show methylation at particular sites.

Cameron et al. (Blood, vol. 94, No. 7, pages 2445-2451, October 1999) teaches the p15 CpG island methylation is heterogeneous. An analysis of the p15 CpG island illustrates that there was marked heterogeneity for the specific CpG sites methylated (abstract). Cameron teaches that the density of methylation within the CpG island and not any specific location correlates between with transcriptional loss (abstract). Cameron teaches that he importance of hypermethylation at 1 or 2 CpG sites and their location relative to transcription start sites remain to be determined (page 2445, col. 1). Thus, Cameron does not support the argument that a single dinucleotide may be representative of the entire CpG island. In fact Cameron teaches that the exact location of methylated sites varied not only between samples but also between alleles from each cancer (page 2447, col. 2).

Guidance in the Specification.

The specification clearly states that "unfortunately, the mere knowledge of the basic existence of altered methylation of CpG dinucleotides within CpG islands of cancer cells relative to normal cells, or of the fact that in particular instances such methylation changes result in altered gene expression (or chromatin structure or stability), is inadequate to allow for effective diagnostic, prognostic and therapeutic application of this knowledge" (page 2, lines 31-35). The specification continues to state "this is because only a limited number of CpG islands have been characterized, and thus there is insufficient knowledge, as to which particular CpG islands, among many, are actually involved in, or show significant correlation with cancer or the etiology thereof. Moreover, complex methylation patterns, involving a plurality of methylation-altered DNA sequences, including those that may have the sequence compositions to qualify as CpG islands, may exist in particular cancers" (page 3, lines 1-5). Therefore, there is a need in the art to identify and characterize specific methylation altered DNA sequences, and to correlate them with cancer to allow for their diagnostic, prognostic and therapeutic application (page 3, lines 7-10). The specification teaches the invention provides for 103 DNA sequences having distinct methylation patterns in cancer, as compared to normal tissue (page 5, lines 35-36). These "methylation-altered DNA sequence embodiments correspond to 103 DNA fragments isolated from bladder and prostate cancer patients" (page 6, lines 1-2). Genomic DNA was isolated from tissue of bladder or prostate cancer patients and identified as either hypermethylated or hypomethylated (page 6). The guidance provided by the specification amounts to an invitation for the skilled artisan to try and follow the disclosed instructions to make and use the claimed invention. The specification merely discloses

Quantity of Experimentation

The quantity of experimentation in this area is extremely large since there is significant number of parameters which would have to be studied. The specification has not taught that a predictable correlation exists between nucleic acids which are "contiguous CpG island sequences that comprise a DNA sequence selected from the group consisting of SEQ ID NO: 36-37". The specification has not described any "a contiguous CpG island sequences that comprise a DNA sequence selected from the group consisting of SEQ ID NO: 36-37", therefore, it is unpredictable that "a contiguous CpG island sequences that comprise a DNA sequence selected from the group consisting of SEQ ID NO: 36-37" are indicative of cancers absent unpredictable and undue experimentation. The skilled artisan would first be required to determine "a contiguous CpG island sequences that comprise a DNA sequence selected from the group consisting of SEQ ID NO: 36-37" and then assay these unknown sequences to determine whether or not they are hypermethylated or hypomethylated and then whether this aberrant methylation status is associated with cancer. Moreover, the art does not support the idea that all contiguous CpG islands are associated with cancer of prostate, colon or breast. For example, in CACNA1G (see Toyota et al. Cancer Research, Vol. 59, pages 4535-4541, September 1999), a detailed analysis was provided for CpG islands within the gene. The eight regions each behaved very differently. For example Regions 1 and 2 behaved in a concordant manner. Region 3 had either no methylation or very low levels of methylation. Regions 5, 6, 7 behaved differently than regions 1-3. Regions 4, 8 behaved differentially again. Thus, with regards to hypermethylation in cancer, the CpG region upstream of CACNA1G appears to be behave independently (page 4538, col. 1). Therefore, since the art provides examples where CpG islands act in predictable ways (cited by applicant) and examples where CpG islands act independently (cited by

examiner, namely Toyota, for example), it is unpredictable whether the instant CpG islands act in a predictable or independent manner.

As noted by Pao, it is not clear that the presence of hypermethylation of a single CpG is indicative of a disorder. Pao and Cameron teach individual sites are not sufficient to assess disease state. Pao further teaches certain normal tissues show some methylation. Thus, the presence of a hypermethylated CpG is not representative of breast cancer, for example. Moreover, the claims are not specifically drawn to hypermethylation compared to normals. The art does not support that the methylation state of a CpG dinucleotide in SEQ ID NO: 36 is not representative of the state of the CpG dinucleotides in the CpG island. The skilled artisan would be required to perform additional experimentation which is unpredictable and undue to determine which CpG island dinucleotides are individually associated with diagnostics. The art, namely Pao and Cameron both support the heterogeneity of individual CpG site methylation.

Neither the art nor the specification support the assertion that a CpG dinucleotide may allow diagnostic or prognostic assays for cancer. Similarly, the specification and the art do not support that a contiguous CpG island sequence that comprises SEQ ID NO: 36 would be similarly methylated.

Therefore, it is unpredictable that regions contiguous with SEQ ID NO: 36-37 or single dinucleotides are associated with cancer. This would require years of inventive effort, with each of the many intervening steps, upon effective reduction to practice, not providing any guarantee of success in the succeeding steps.

Level of Skill in the Art

The level of skill in the art is deemed to be high.

Conclusion

In the instant case, as discussed above, in a highly unpredictable art where the art teaches not all dinucleotides are representative of the methylation over the sequence and normal sequences contain some normally methylated dinucleotides to diagnosis cancer based upon dinucleotides. Further, the prior art and the specification provides insufficient guidance to overcome the art recognized difficulties. Moreover, the declaration filed by applicants indicates a hypermethylation. The declaration is not directed to particular dinucleotides. Thus, the results showed in the declaration are not commensurate in scope with the claimed invention. Thus given the broad claims in an art whose nature is identified as unpredictable, the unpredictability of that art, the large quantity of research required to define these unpredictable variables, the lack of guidance provided in the specification, the absence of a working example and the negative teachings in the prior art balanced only against the high skill level in the art, it is the position of the examiner that it would require undue experimentation for one of skill in the art to perform the method of the claim as broadly written.

Response to Arguments

The response traverses the rejection. The response asserts that the claims have been adequately enabled. In responding to the examiner's rejection, applicants have set forth several reasons for traversal which will be addressed in the order argued.

First, the affidavit under 37 CFR 1.132 filed May 23, 2003 is insufficient to overcome the rejection of claims 1-2, 4, 7-12 based upon enablement as set forth in the

last Office action. The declaration filed by Dr. Cathy Lofton-Day of May 23, 2003 has been thoroughly reviewed, but found not persuasive to enable the full scope of the instant claims. Moreover, the declaration filed by applicants indicates a hypermethylation. The declaration is not directed to particular dinucleotides. Thus, the results showed in the declaration are not commensurate in scope with the claimed invention. The declaration is drawn to SEQ ID NO: 36 and 37.

The response states that the "relevant question is whether the CpG dinucleotide sequences within a given CpG island behave coordinately." This appears to be the remaining question in this application.

The response asserts that Toyota is directed to CpG methylation between islands and not within islands. The response asserts that the subregions within a given CpG island behave coordinately (page 8 of response filed October 19, 2007). This assertion does not appear to be supported by the text of Toyota. It is agreed that Toyota teaches examples were CpG islands act independently. However, Toyota, as pointed out by the response does teach different subregions within a given CpG island such as regions 5-7 of island 2. Toyota specifically teaches that regions 5, 6,7 behaved quite differently than did regions 1-3. Methylation of these regions was less frequent than in regions 1 and 2: 22 of 36 cell lines had no detectable methylation there, despite often showing methylation of region 1 and 2. However, when methylation was present (in 13 of 36 cell lines), it affected all three regions simultaneously, although to varying extents. This illustrates that the different dinucleotides within at least one DNA sequence that of an island do not necessarily share coordination in their methylation

patterns (page 4538, col. 1). Moreover, Toyota specifically teaches that regions 3, 4, and 8 correspond to the edge of the CpG islands and behave a little differently than the hearts of the CpG islands (page 4538, col. 1). Thus, it is clear that the response is asserting that the instant SEQ IDN O: 36 and 37 are partial islands and may contain additional sequences on either side. However, it is unclear how far down the genome each island may stretch. Further it is unclear where the edge of the islands lie and whether these CpG sites behave a little differently than the hearts of the CpG island. It is unclear whether SEQ ID NO: 36 and 37 are in the heart of the island or whether they are on the edge. Thus, it is not predictable that all CpG dinucleotides within the claimed regions would behave in similar manners as argued by the response.

The response asserts that the teachings of Pao do not run counter to applicants recitation of coordinately methylated CpGs. It is noted that the claims do not require coordinately methylated at this time. The claims require determining the methylation state of a CpG dinucleotide and determining a diagnosis or prognosis based upon methylation which is hypermethylation compared to a control. This is unpredictable because Pao is replete with examples in Figure 2 of situations where a particular CpG site is hyper and hypomethylated compared to "normals" for any particular sample (see CpG-130 for bladder tissue). Moreover across samples at different positions, there are numerous examples where all levels of methylation are found (see "normal" sample 90). Thus, it is unpredictable whether a single CpG dinucleotide is predictive diagnosis or prognosis of breast cancer. As discussed at length above, p156 and EDNRB are very specific example of contiguous regions within the same CpG island which do not share

hypermethylation. To determine which regions are and which regions are not associated with cancer requires further undue and unpredictable experimentation. The specification does not provide any guidance in determining which sequences are associated without performing the further unpredictable and undue experimentation. The claims state that the "state of a CpG dinucleotide" is determined and the prognosis or diagnosis is determined by the detection of hypermethylation. It is unpredictable which CpG sites may be used for analysis and which sites do not provide any guidance to the diagnosis or prognosis. As discussed above for Pao, since there is heterogeneity across a CpG region, the skilled artisan would be unable to assay for a single CpG dinucleotide and provide a diagnosis or prognosis for breast cancer, for example. Even, applicant's own work, as set forth in the declaration filed in 2003 illustrates analysis over a larger region. The art of Pao and Cameron support the position that dinucleotides are heterogeneously methylated.

Finally, the response provides a declaration by Dr. Kurt Berlin. The declaration filed by Dr. Kurt Berlin, February 8, 2007 has been thoroughly reviewed. It is noted that Dr. Kurt Berlin's declaration appears to be directed to SEQ ID NO: 46 and 47. The instant claims are drawn to SEQ ID NO: 36 and 37. Thus, it is not clear how the declaration speaks to the instant claims.

The response asserts that the declaration describes a paper further confirming as was appreciated in the art at the time of filing that there is a significant correlation for co-methylation within CpG regions. It is noted that the paper filed by the response and

declaration was available approximately 6 years after the filing of the instant application. Moreover, the paper cited, specifically states that "our data suggest DNA methylation to be ontogenetically more stable than previously thought." Which further suggested that this paper may show data which moves away from previously understood mechanisms. Thus, it is not clear that at the time the invention was made, namely 2000, the art appreciated any correlation for comethylation within CpG dense regions.

Moreover, the data illustrated in the Eckhardt reference appears to be a profiling of normal human chromosomes and does not appear to be directed at differential methylation upon cancer progression or occurrence. Thus, it is not clear that the cited article is directed to diagnostic or prognostic analysis.

Thus for the reasons above and those already of record, the rejection is maintained.

Conclusion

6. No claims allowable.

7. This is a RCE of applicant's earlier Application No. 09/699,243. All claims are drawn to the same invention claimed in the earlier application and could have been finally rejected on the grounds and art of record in the next Office action if they had been entered in the earlier application. Accordingly, **THIS ACTION IS MADE FINAL** even though it is a first action in this case. See MPEP § 706.07(b). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no, however, event will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

8. Any inquiry concerning this communication or earlier communications from the examiner should be directed to examiner Jeanine Goldberg whose telephone number is (571) 272-0743. The examiner can normally be reached Monday-Friday from 7:00 a.m. to 4:00 p.m.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ram Shukla, can be reached on (571) 272-0735.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

The Central Fax Number for official correspondence is (571) 273-8300.

J. Goldberg

Jeanine Goldberg
Primary Examiner
December 27, 2007